

Remarks/Arguments

Amendment to the Claims

Claims 7, 16-18 are pending upon entry of the amendments.

Claim 7 has been amended.

No new matter has been added

35 U.S.C. §112, 1st paragraph

The Examiner has rejected Claims 7 and 16-18 under 35 U.S.C. 112, first paragraph, because the specification, *"while being enabled for a method of screening for a candidate compound that antagonizes or agonizes a GPR4 related polypeptide comprising the amino acid sequence of SEQ ID NO: 3, does not reasonably provide enablement for a method for screening for a candidate compound that antagonizes or agonizes a GPR4 related polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:3."* The Examiner states that in view of the nature of complexity of the work and unpredictability of the art, it would take undue experimentation for one skilled in the art to make and use the claimed methods of polypeptides without sufficient guidance. The Examiner further states that since there is no functional limitation or any particular conserved structure recited in the claims, the method recites an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to make and/or use. The Applicants disagree and traverse the rejection.

It is well settled that, to satisfy the enablement requirement, the specification must provide sufficient disclosure in combination with the general knowledge and skill in the art to permit the skilled artisan to make and use the invention without resorting to undue experimentation. The test for enablement is not whether any experimentation is necessary, but if experimentation is necessary, whether it is undue. The fact that the experimentation may be complex or extensive, does not make it undue, if the art typically engages in such experimentation. Furthermore, the presence of inoperable embodiments within the scope of a claim does not necessarily render a claim non-enabled. Indeed, inoperable embodiments are permitted within the scope of a claim provided that one of skill in the art could determine which embodiments were operative with expenditure of no more effort than is normally required in the art.

With respect to a conserved structure, the claims require that the recited polypeptides comprise at least 95% sequence identity to the sequence of SEQ ID NO: 3. Thus, at a minimum, the claimed genus has at least 95% structural conservation with fully disclosed and characterized sequence. Furthermore, the specification clearly identifies human GPR4 polypeptide (i.e.: SEQ ID NO: 3) as a member of the G-protein coupled receptor (GPCR) family.

There are several conserved structural features characteristic of this family, that are well known to those skilled in the art. In addition, at the time of filing the present application the crystal structure of the related rhodopsin GPCR had been elucidated and could be used as an experimental model and structural template for comparison with other GPCRs to determine secondary structures and highly conserved amino acids (Palczewski et al., *Science*, (2000) 289:739). Key structural features present in the GPCR family are also present in the human GPR4 polypeptide which would direct one to regions of the receptor that could be modified to retain function. These features include: seven hydrophobic trans-membrane domains, several intra- and extra-cellular loops, an extracellular N-terminus, and intracellular carboxy terminus (Mahedevan, et al., *Genomics* (1995) 30:84). More specifically, for example, the cysteine residues present in the first and second extracellular loops of GPR4 are present in almost all members of this superfamily (Mahedevan, et al., *Genomics* (1995) 30:84) and have been shown to be important for proper receptor structure and function (Savarese, et al., *Biochem J* (1992) 283:1). In addition, it has been noted that conserved polar residues within the predominantly hydrophobic trans-membrane domains play an important role in protein folding and structure (Savarese, et al., *Biochem J* (1992) 283:1). Thus, there was considerable knowledge and sufficient guidance in the art which would direct one of skill to the portions and structural features of GPR4 which might be critical for activity, as well as what features could be modified that would result in a polypeptide with the same function as GPR4 and sequence at least 95% identical to SEQ ID NO:3.

With respect to functional limitations of a GPR4 related polypeptide, newly amended Claim 7 includes a functional limitation whereby a GPR4 related polypeptide with at least 95% sequence identity to SEQ ID NO: 3 activates cAMP formation in response to pH conditions that stimulate GPR4. Support for this amendment may be found in the specification and claims as originally filed, and at least at page 41 paragraph 2. Thus, the specification clearly discloses that human GPR4 polypeptide of SEQ ID NO: 3 is a GPCR which activates the formation of cAMP when stimulated by a changing pH. The specification describes a cAMP formation assay (Example 9, page 40) which could easily be used by one of skill in the art to measure the function of GPR4 and GPR4 related polypeptides with at least 95% identity to SEQ ID NO:3 and determine which polypeptides with 95% identity to SEQ ID NO:3 were operable and retained the recited function of a GPR4 related polypeptide. Thus, as amended, the instant claims recite a method utilizing a genus of GPR4 related polypeptides, each species of which has a conserved structure and is required to satisfy a specific functional requirement, namely, activation of cAMP formation in response to pH conditions that stimulate GPR4. The instant disclosure and state of the art at the time of filing provided sufficient guidance as to conserved structural features of the claimed polypeptides, to permit one of skill in the art to readily identify, using the cAMP formation assay described in the specification, those polypeptides having at least 95% conserved structure compared to SEQ ID NO: 3 that also satisfy the functional requirement

recited in the amended claims. Applying such an assay to polypeptides with at least 95% identity to SEQ ID NO:3 would not require undue experimentation. Once the functionality of the variant protein is confirmed, it can be used in the screening assay disclosed in Example 10 on page 41 of the application as filed.

Thus, there was sufficient direction and guidance in the specification, in combination with a high level of skill in the art, to permit one of skill in the art practice the invention without engaging in undue experimentation.

Applicants respectfully request that the rejection be reconsidered and withdrawn and the remarks made herein be entered and made of record in the file history of the present application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,



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